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The genetics of common epilepsies: common or distinct?

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See Articles page 893

In *The Lancet Neurology,* the International League Against Epilepsy Consortium on Complex Epilepsies[1] reports the first meta-analysis of genome-wide association studies (GWAS) in common epilepsies, following a route of large-scale collaborations familiar to many other groups of chronic diseases. The study brings together 12 separate datasets from three continents and diverse ethnic origins ranging from Chinese to Finnish. The analysis poses a philosophical question: can genetic factors be identified when the 30 or so different epilepsy syndromes are collapsed together or crudely considered as generalised or focal types?

The results of the Consortium's lumping strategy to investigate more than 2600 cases of generalised epilepsy and 5300 cases of focal epilepsy contain some surprises, raise some questions, and will stimulate debate about the future of the genetics of common epilepsies. Single nucleotide polymorphisms in *SCN1A*, a gene implicated in many different rare epilepsies (including Dravet syndrome), emerged as factors with genome-wide significance within a dataset that included generalised, focal, and unclassified epilepsies. Two new candidate loci, one for all epilepsy at 4p15.1 (possibly implicating a protocadherin, *PCDH7*) and another for genetic generalised epilepsy at 2p16.1, also emerged, and await definitive gene identification. The analysis provides support for the 2p16.1 locus, an earlier finding by the EPICURE partners for genetic generalised epilepsy,[2] but no support for another EPICURE genetic generalised epilepsy locus at 17q21. Genome-wide significance was not attained for single nucleotide polymorphisms common to focal epilepsies.

These results are of most importance for the genetic generalised epilepsies, for which findings from genetic epidemiological studies have repeatedly shown that different generalised epilepsies have high heritability and share genetic factors.[3] By comparison, focal epilepsies have not shown similar levels of heritability,[3] nor has evidence from genetic epidemiological studies suggested shared genetic factors (with the exception of rare examples such as *GRIN2A* and *DEPDC5* among idiopathic and familial focal epilepsies[4,5]). This meta-analysis therefore goes some way towards answering the question of shared factors, but are we any closer to understanding the specificity of these genes with respect to epilepsy subtypes?

GWAS work best when there is little phenotypic, ethnic, and allelic heterogeneity in the dataset. Yet this meta-analysis forced together different types of epilepsy with different case definitions from different ethnic populations—almost inevitable in retrospective collaborations of this size. Heterogeneity can be problematic for interpretation of results from genome-wide analyses. Different effect sizes could legitimately exist across groups, or effect sizes could differ because of different linkage disequilibrium structures (such as might be observed in an analysis of individuals with mixed ethnic origins). Random-effects meta-analyses are appropriate in these settings, and can maintain or improve power.[6] Although assessment is difficult in the absence of cohort-specific QQ-plots, findings from this study suggest that the association test statistics might deviate from model assumptions; population structure could be one explanation, although a mixed model framework was used. Other reasons for the possible deviations might be the use of linear mixed models for a binary outcome, or the choice of a fixed-effects meta-analysis. The source of this deviation requires some

investigation. In any event, there is contribution at the identified loci across more than one cohort, but the extent and nature of the overall association remains unclear.

Heterogeneity is often the price paid for assembly of huge sample sizes for GWAS or meta-analyses. However, the power of GWAS can be boosted not only by increasing sample size, but also in creative ways that exploit previous biological knowledge. For example, findings from many studies have suggested an important role for $GABA_A$ receptor function in genetic generalised epilepsies,[7] and techniques such as genome-wide pathway and hypothesis-driven analyses[8] can be exploited to test such specific hypotheses and generate potential therapeutic targets. Another approach that sidesteps the complications of phenotype integrity is the use of imaging endophenotypes; changes in structural connectivity and grey matter volume have already been identified in juvenile myoclonic epilepsy.[9] Quantitative measures closer to the underlying biology than the clinical phenotype might also reduce required sample sizes to the hundreds with newly developed mathematical methods,[10] while improving specificity of findings.

Knowledge of the genetics of common epilepsies is in need of integration. Strong but rare risk factors in the form of recurrent copy-number variation are known, and researchers have understood for some time that there are distinct genetic influences on absence and myoclonic seizure types within the genetic generalised epilepsies.[11] We openly speak of complex models for common epilepsies, but recent efforts have been largely in search of rare monogenic causes, or single common variants for heterogeneous phenotypic groupings. A change in research strategy towards use of more specific phenotypes (that are guided by family studies of phenotype coaggregation in epilepsy syndromes, or by endophenotypes), and modelling of complexity in studies of the genetic architecture of these phenotypes, would serve to reduce heterogeneity and identify genes for specific syndromes, seizures, and comorbid traits. Such studies, hand-in-hand with epigenetics and other omics methods, could offer a way to account for individual patient differences in presentation, comorbidity, and prognosis.

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Lost in space: sleep

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See Articles page 904

Space is one of the most hostile environments. Sufficient sleep duration and quality are crucial to ensure performance and prevent fatal errors and accidents in space. Data on astronauts' sleep in space are scarce, but in *The Lancet Neurology*, Laura Barger and colleagues[1] report findings from their study assessing 4267 days of actigraphically measured sleep in 85 astronauts during Space Shuttle or International Space Station (ISS) missions.

Sleep averaged 5·96 h (SD 0·56) during shuttle missions, 6·09 h (0·67) during ISS missions, and